REMARKS/ARGUMENTS

The Pending Claims

Claims 1, 3, 4, 7, and 11-13 are currently pending and are directed to a method for the therapeutic treatment of a cancer in a mammal.

The Amendments to the Specification and Abstract

The specification has been amended to indicate that the parent U.S. Patent Application No. 09/600,826 has issued as U.S. Patent 6,770,742, and to correct matters of form. The abstract has been amended to more accurately reflect the claimed subject matter and to shorten its length. No new matter has been added by way of these amendments.

The Amendments to the Claims

The claims have been amended to point out more particularly and claim more distinctly the present invention. Claim 1 has been amended to incorporate the subject matter of claims 2, 5, 6, 8-10, and 14. As a result, claims 2, 5, 6, 8-10, and 14 have been cancelled. Claims 3, 7, 11, and 13 have been amended to change claim dependencies and to correct matters of form. Claim 11 also has been amended to recite that the mutation occurs at amino acid position 388 in an FGFR-4 protein having the amino acid sequence of EMBL Gene Bank accession number X57205. This amendment is supported by the specification at, e.g., page 9, lines 17-20. Claims 15-29 have been cancelled as being drawn to a non-elected invention in response to a restriction requirement. Applicants reserve the right to pursue any cancelled subject matter in a continuation, continuation-in-part, divisional, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter. No new matter has been added by way of these amendments.

The Office Action

The Office Action raises the following concerns:

(a) the specification is objected to for failing to indicate that the parent application has issued as a patent,

(b) the Information Disclosure Statement filed on August 27, 2003 allegedly does not comply with 37 C.F.R. §§ 1.97 and 1.98 and M.P.E.P. § 609 because certain references were not submitted to the Patent Office,

(c) claims 1-14 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite,

(d) claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement,

(e) claims 1-11, 13, and 14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description, and

(f) claims 1-3 and 5 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Takahashi et al., *FEBS Letters*, *288*: 65-71 (1991) ("the Takahashi reference").

Reconsideration of these objections and rejections is respectfully requested.

Discussion of Objections to Specification and IDS

The Office Action objects to the specification for failing to indicate that the parent application has issued as a patent. The specification has been amended to indicate that U.S. Patent Application No. 09/600,826 issued as U.S. Patent 6,770,742, thereby rendering this objection moot.

The Office Action objects to the IDS filed on August 27, 2003 because reference AK allegedly was not submitted with the IDS, and no translation of the abstract or explanation of relevance for reference AQ was submitted with the IDS. Submitted herewith is an IDS including a copy of reference AK and an English translation of the abstract for reference AQ.

Discussion of Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-14 are rejected under Section 112, second paragraph, as allegedly indefinite. Claims 2, 5, 6, 8-10, and 14 have been cancelled, thereby mooting the Section 112, second paragraph, rejections as to those claims.

Claim 1 allegedly is indefinite because it is not clear whether the "inhibitor of FGFR-4" refers to the FGFR-4 gene or FGFR-4 protein. Claim 1 has been amended such that it is more clear that the term "inhibitor of FGFR-4" refers to the FGFR-4 protein.

Claim 7 recites "wherein the mutation is one or several point mutations," and is allegedly indefinite because claim 6, from which claim 7 depends, recites "a mutation." Claim 7 has been amended to depend from claim 1, which recites that the mutated FGFR-4 comprises *at least one* point mutation in the transmembrane domain of FGFR-4. Thus, claim 7 also has been amended to recite "wherein the *at least one* mutation is one or several point mutations."

Claim 11 allegedly is indefinite because it does not refer to a specific FGFR-4 sequence in which amino acid 388 is mutated. Claim 11 has been amended to recite that the FGFR-4 mutation occurs at amino acid position 388 in an FGFR-4 protein having the amino acid sequence of EMBL Gene Bank accession number X57205.

In view of the foregoing, the rejections under Section 112, second paragraph, are moot and should be withdrawn.

Discussion of Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-14 are rejected under Section 112, first paragraph, as allegedly lacking enablement. Claims 1-11, 13, and 14 are rejected under Section 112, first paragraph, as allegedly lacking written description. Because claims 2, 5, 6, 8-10, and 14 have been cancelled, the Section 112, first paragraph, rejections will be addressed as they pertain to claims 1, 3, 4, 7, and 11-13.

a. Enablement

The Office Action alleges that the pending claims are not enabled as to the prophylactic treatment of RTK hyperfunction-induced disorders, and as to the scope of the term "inhibitor of fibroblast growth factor receptor-4 (FGFR-4)."

Solely in an effort to advance prosecution of the subject application, and not in acquiescence of the rejection, claim 1, as amended, no longer recites a method for the prophylactic treatment of RTK hyperfunction-induced disorders. Rather, claim 1 is now

directed to a method for the therapeutic treatment of cancer. As such, the enablement rejection with respect to the prophylactic treatment of RTK hyperfunction-induced disorders is moot and should be withdrawn.

The Office Action contends that the claims, given their broadest reasonable interpretation, are directed to a method of treatment encompassing an inhibitor of wild-type FGFR-4 and any mutated variant thereof. The Office Action further alleges that the only FGFR-4 mutation disclosed in the specification as predisposing a mammal to cancer is a glycine to arginine substitution at amino acid position 388 of the wild-type FGFR-4 sequence ("G388R mutation"). Thus, the Office Action concludes that undue experimentation would be required to generate and identify the "infinite number" of FGFR-4 variants, other than the G388R mutant, which correlate with an increased risk of cancer.

Claim 1, as amended, is directed to a method for the therapeutic treatment of a cancer in a mammal wherein (i) the mammal comprises a mutated fibroblast growth factor receptor-4 (FGFR-4) protein, and (ii) the mutated FGFR-4 comprises at least one point mutation in the transmembrane domain of FGFR-4 that substitutes a hydrophilic amino acid for a hydrophobic amino acid, which method comprises administering to the mammal an effective amount of at least one inhibitor of the mutated FGFR-4, wherein the cancer in the mammal is treated. Therefore, claim 1 recites a specific type of amino acid substitution, i.e., substitution of a hydrophilic amino acid for a hydrophobic amino acid, within a specific defined region of the FGFR-4 protein, i.e., the transmembrane domain. One of ordinary skill in the art at the time the subject application was filed was well aware of which amino acids are hydrophilic, and which amino acids are hydrophobic. In addition, the amino acid sequence of the transmembrane domain of FGFR-4 was known in the art at the time the subject application was filed, and is disclosed in the specification as SEQ ID NO: 2. The amino acid sequence of the transmembrane domain is set forth below, with the hydrophobic amino acid residues bolded and underlined:

R<u>Y</u>TD<u>IILYA</u>S<u>G</u>S<u>LALAVLLLLAG</u>L<u>Y</u>

Thus, one of ordinary skill in the art need only identify a modification of at least one of only several amino acid residues in an FGFR-protein to practice the method defined by claim 1. As such, amended claim 1 does not encompass an "infinite number" of FGFR-4 variants as

alleged by the Office Action, and any experimentation required to practice the invention defined by claim 1 would be routine at most, and certainly not undue.

In view of the foregoing, claim 1, and claims 3, 4, 7, 11-13 depending therefrom, are enabled and the Section 112, first paragraph, rejection should be withdrawn.

b. Written Description

The Office Action contends that the claims, given their broadest reasonable interpretation, are directed to a method of treatment encompassing inhibition of wild-type FGFR-4 or any mutated variant thereof. According to the Office Action, the specification does not describe inhibition of the genus of FGFR-4 polypeptides encompassed by the claims, but only describes inhibition of an FGFR-4 polypeptide comprising a glycine to arginine substitution at amino acid position 388.

As discussed above, claim 1 has been amended to recite a method for the therapeutic treatment of a cancer in a mammal wherein (i) the mammal comprises a mutated fibroblast growth factor receptor-4 (FGFR-4) protein, and (ii) the mutated FGFR-4 comprises at least one point mutation in the transmembrane domain of FGFR-4 that substitutes a hydrophilic amino acid for a hydrophobic amino acid, which method comprises administering to the mammal an effective amount of at least one inhibitor of the mutated FGFR-4, wherein the cancer in the mammal is treated. Therefore, claim 1 recites a specific type of amino acid substitution, i.e., substitution of a hydrophilic amino acid for a hydrophobic amino acid, within a specific defined region of the FGFR-4 protein, i.e., the transmembrane domain. One of ordinary skill in the art at the time the subject application was filed was well aware of which amino acids are hydrophilic, and which amino acids are hydrophobic; the specification need not disclose that which is well known to one of ordinary skill in the art. See M.P.E.P. 2163 and *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 U.S.P.Q. at 94. In addition, the amino acid sequence of the transmembrane domain of FGFR-4 is disclosed in the specification as SEQ ID NO: 2. Therefore, one of ordinary skill in the art would recognize that Applicants has possession of the invention defined by amended claim 1 at the time the subject application was filed.

The Office Action also alleges that the specification does not adequately describe the genus of RTK hyperfunction-induced disorders. In this respect, the Office Action contends that the only RTK hyperfunction-induced disorder associated with mutations in the FGFR-4 polypeptide disclosed in the specification is cancer. Solely in an effort to advance prosecution of the subject application, and not in acquiescence of the rejection, claim 1 has been amended such that it is directed to a method of treating cancer in a mammal.

In view of the foregoing, the subject matter of claim 1, and claims 3, 4, 7, and 11-13 depending therefrom, is adequately described in the subject application. Accordingly, the written description rejection should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 102(b)

Claims 1-3 and 5 are rejected under Section 102(b) as allegedly anticipated by the Takahashi reference. The Takahashi reference allegedly discloses subcutaneous administration of a neutralizing antibody against human FGF to nude mice bearing human glioblastoma cells, which results in suppression of tumor development in the mice.

Claim 1, as amended, is directed to a method for the therapeutic treatment of a cancer in a mammal wherein the mammal comprises a mutated fibroblast growth factor receptor-4 (FGFR-4) protein. The mammals treated by the method disclosed in the Takahashi reference do not comprise a mutated FGFR-4 protein. Moreover, the glioblastoma cell lines transplanted into the nude mice do not comprise a mutated FGFR-4 protein. As such, the Takahashi reference does not disclose the subject matter of claim 1, or claims depending therefrom, and the Section 102(b) rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,

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